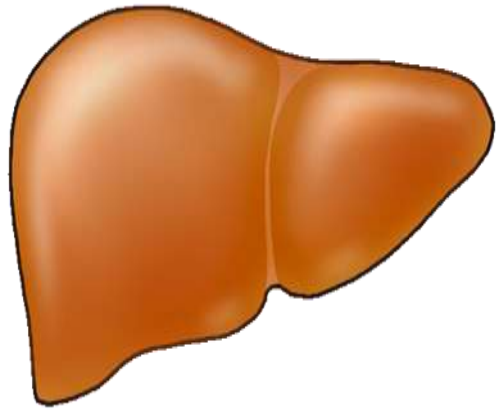
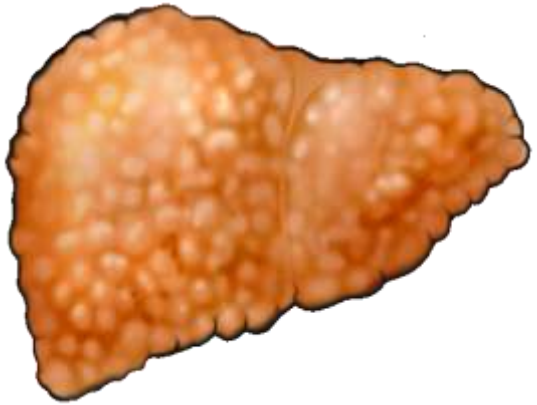
بسم الله الرحمن الرحيم

March 16th, 2016

Metabolic Indications of Liver Transplantation





Ehab Abdel-Khalek

Professor of Internal Medicine,

Hepatology & Gastroenterology,

Consultant of Liver Transplantation

Mansoura University

History of the Procedure

1960 Dr. T.E. Starzl started research in dogs.

1963 Starzl attempted the first human LT. Denver, CO, USA.

1967 The first successful LT.

1970 Dismal survival rates, approxim. 15% at 1-year F.U. (immunosuppressive regimen largely based on steroids and azathioprine)

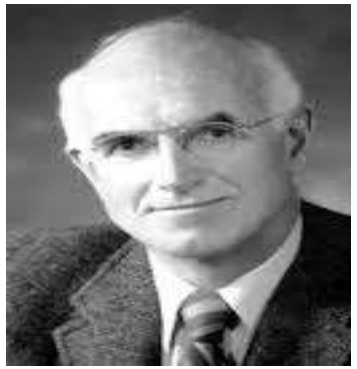
1980 A clinical reality after the discovery of cyclosporine.

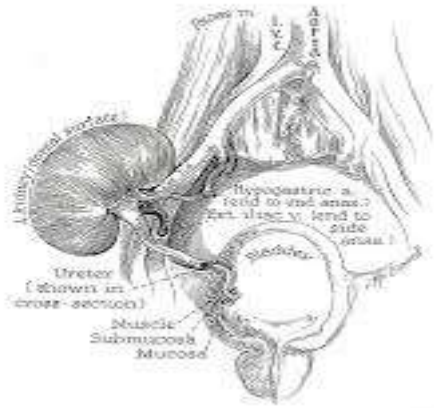
1983 USNIH: LT is a definitive therapy for ESLD out of the experim. realm.

Starzl, et al. Surg Gynecol Obstet ,117: 659–76 (1963)

Kidney

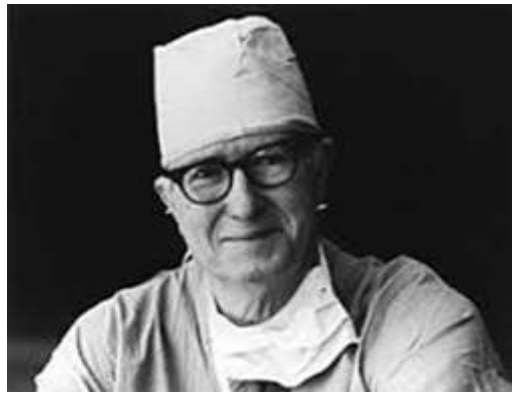
- The first successful kidney transplantation by Dr. Joseph Murray, 1954, Boston, MA, USA.
- 2 identical twins.
- The Nobel prize 1990.





Lung

- 1963
- Dr. J. D. Hardy
- Jackson, MS.



Heart

- 1967
- Dr. C. N. Bernard.
- Cape Town, SA.

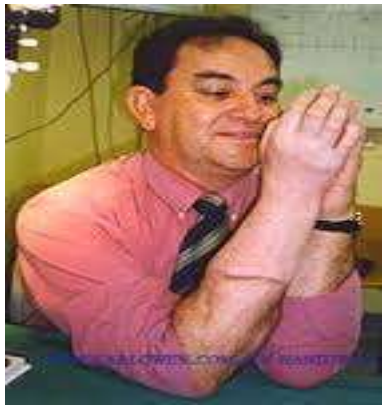
Fig. 2. Christiaan Barnard.

Heart

- 1967
- Dr. C. N. Bernard.
- Cape Town, SA.

Hand

- 1998
- J-M. Dubernard.
- Amiens, France.



Face

- 2005
- J-M. Dubernard.
- Amiens, France

Jean-Michel Dubernard.
Amiens, France

Hand
1998

Face
2005

Metabolic Indications of Liver Transplantation

Metabolic liver disease comprises a broad spectrum of liver diseases that may include:

Hepatic manifestations of systemic disease (e.g. NASH).

Diseases primarily affecting the liver (i.e. Wilson's disease, Hemochromatosis, glycogen storage disease).

Diseases that are based on metabolic defects in the liver but manifest extrahepatically (e.g. familial amyloidotic polyneuropathy, Primary hyperoxaluria type 1).

Liver transplantation for metabolic diseases of the liver is more common for pediatric patients than for adult patients, comprising about 20% of pediatric liver transplantation.

Metabolic disorders that may be indications for liver transplantation

- Alpha-1-antitrypsin deficiency
- Hemochromatosis
- Wilson’s disease
- Nonalcoholic fatty liver disease
- Cystic fibrosis
- Tyrosinemia
- Progressive familial intrahepatic cholestasis (Alagille, Bylers syndrome)
- Erythropoietic protoporphyria
- Urea cycle enzyme deficiencies
- Glycogen storage disease III, IV
- Crigler–Najjar syndrome, type 1
- Hemophilia A
- Homozygous hypercholesterolemia
- Protein C deficiency
- Galactosemia
- Familial amyloidosis
- Hereditary oxalosis

Metabolic disorders that may be indications for liver transplantation

- Nonalcoholic fatty liver disease
- Hereditary hemochromatosis
- Wilson’s disease
- α 1 - antitrypsin deficiency
- Familial amyloidotic polyneuropathy
- Glycogen storage disease type 1A
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Metabolic disorders that may be indications for liver transplantation

- **Nonalcoholic fatty liver disease**
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Nonalcoholic Fatty Liver Disease (NAFLD)

Hepatitis C virus (HCV) infection-associated end-stage liver disease is the leading indication for liver transplantation worldwide.

Surg Case Rep. 2015 Dec;1(1):124.

In the USA, approximately 5000 liver transplantations are performed annually with HCV accounting for approximately 40% of all cases.

BMJ Open Gastroenterol. 2016 Jan 4;3(1)

Nonalcoholic Steatohepatitis (NASH) is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. It is expected to become the leading indication for liver transplantation in the next 10-20 years.

Robert J et al. J Gastroenterology 2015;148(3):547-555

NAFLD

NAFLD is a term that encompasses a spectrum of hepatic histologic manifestations for conditions ranging from simple steatosis to NASH with or without progressive fibrosis.

NASH is closely related to the prevalence of obesity and the metabolic syndrome.

J Clin Gastroenterol 2014: 48(6)

NAFLD, Pathogenesis

The pathogenesis of NASH involves multiple pathologic pathways related to:

- **Insulin resistance.**
- **Hyperinsulinemia.**
- **Oxidative stress.**
- **Activated inflammatory cytokines.**

NAFLD, Pathogenesis

Metabolic syndrome predicts the presence of steatohepatitis in patients with NAFLD and can therefore be used to target patients for a liver biopsy.

BMJ Open Gastroenterol. 2016 Jan 4;3(1)

NAFLD, Diagnosis

Most patients with NAFLD are asymptomatic or have non specific symptoms.

Ultrasonography is often performed with a sensitivity and specificity rates of 90% and 97%, respectively.

NAFLD, Diagnosis

Liver biopsy is the most accurate way to differentiate between the stages of NAFLD.

Magnetic resonance elastography is a relatively sensitive and specific tool for non-invasive assessment of NAFLD.

Surg Case Rep. 2015 Dec;1(1):124.

NAFLD and liver transplantation

Patients with end-stage liver disease related to NASH are often morbidly obese, which has led to a significant debate about the concomitant risks of OLT.

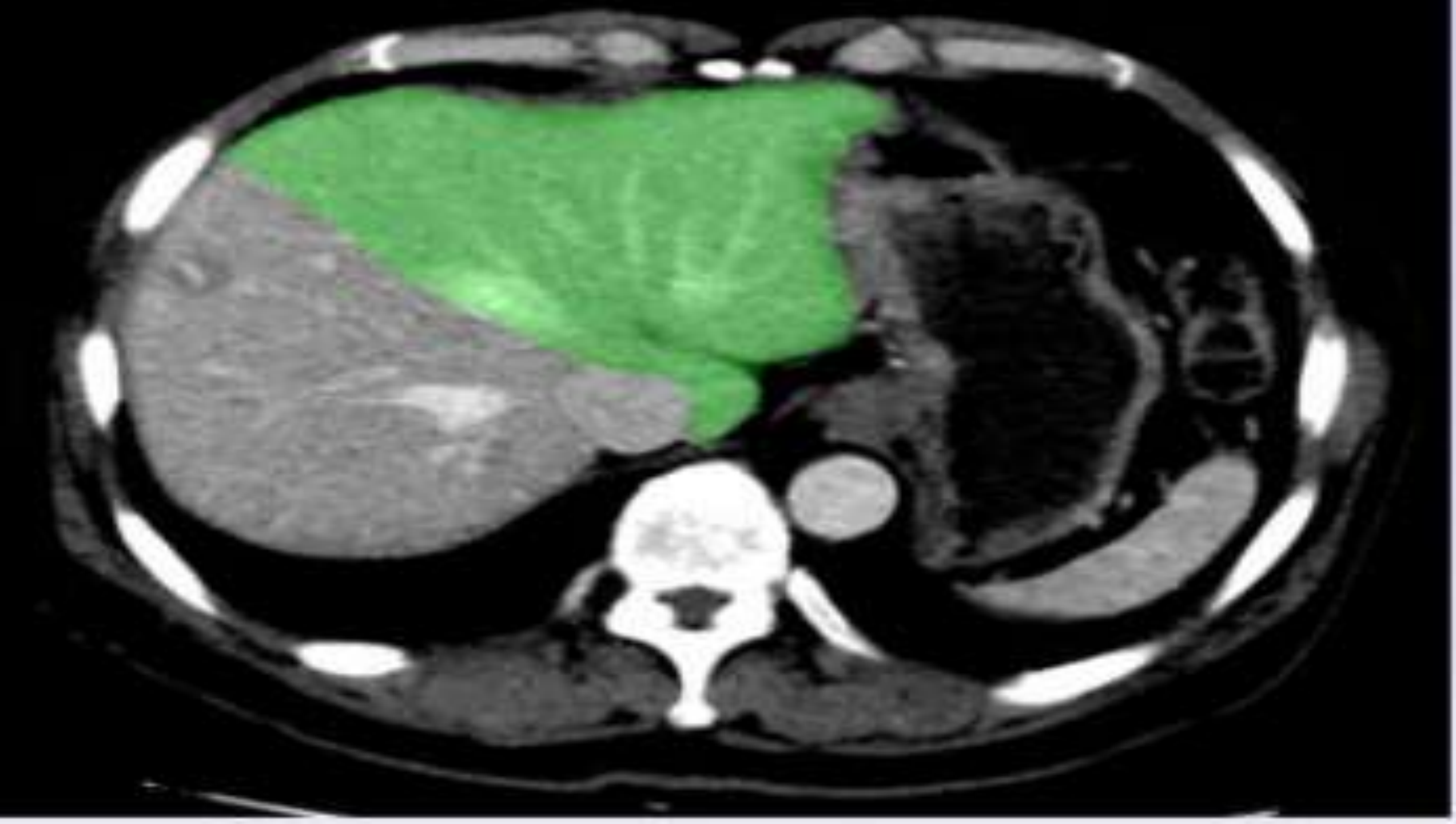
CT volumetric measurement of the potential donor

CT volumetric measurement of the liver of all potential donors.

The outline of the liver lobes selected for transplantation is marked.

Segmentation is carried out along the plane of the middle hepatic vein.

Limanond P et al. Radiology 2004;230(1):276–280



Graft : Recipient weight ratio (GRWR) must be ≥ 0.8 %.

Residual volume must be ≥ 30 %.

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Hereditary Hemochromatosis

Hereditary hemochromatosis, Background & Definition

HH is an autosomal recessive disorder characterized by deposits of iron in tissue and organs, including the liver.

Hereditary hemochromatosis, Diagnosis

Clinical manifestations in HH are related to iron overloading and include:

Liver cirrhosis

Diabetes mellitus

Cardiomyopathy

Hypogonadotrophic hypogonadism

Hypothyroidism

Destructive arthritis

Fatigue

Arthropathy.

J Gastroenterol Hepatol. 2016 Feb

Hereditary hemochromatosis, Diagnosis

A transferrin-saturation (serum iron divided by the serum total iron-binding capacity) of > 45% raises the possibility of HH.

Liver disease is almost only seen in patients with ferritin levels > 1000 ng/ml.

J Endocrinol Invest. 2016

Hereditary hemochromatosis, Diagnosis

Liver biopsy:

Measurement of the hepatic iron concentration (HIC, expressed as micrograms/micromoles of iron per gram dry weight of liver).

The hepatic iron index can then be calculated by dividing HIC by the age of the patient, to adjust for increasing liver iron stores with increasing age in HH.

Normal values are <1.0.

Hereditary hemochromatosis, Diagnosis

Another diagnostic test for HH is measuring iron excretion during phlebotomy, which can be helpful if liver biopsy can not be performed.

Hereditary hemochromatosis, Management and Liver Transplantation

Patients who start iron-depleting therapy (phlebotomies) before the onset of cirrhosis and diabetes have a comparable survival to that of the general population.

Int J Hematol. 2016 Mar

Metabolic disorders that may be indications for liver transplantation

- Nonalcoholic fatty liver disease
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Wilson’s disease

Wilson’s disease

Also known as hepatolenticular degeneration.

Autosomal recessive disease.

Abnormal hepatocyte copper transport with copper deposition in multiple organs, including the liver and brain.

Br J Pharmacol. 2016 Feb 18

Diagnosis

Reduced serum ceruloplasmin.

Increased urinary copper excretion.

Kaiser-Fleischer (KF) rings.

Increased quantitative levels of copper in liver tissue.

Hepatic copper content of ≥ 250 µg/g dry weight is diagnostic for WD.

Management and liver transplantation

Adequate treatment with D-penicillamine can reverse hepatic, neurologic, psychiatric, and ocular manifestations of WD.

With adequate treatment, the progression of liver disease can be halted or reversed. SO, LT for chronic liver disease is not common and the main indication for LT in WD is acute liver failure.

Br J Pharmacol. 2016 Feb 18

Metabolic disorders that may be indications for liver transplantation

- Nonalcoholic fatty liver disease
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- Familial amyloidotic polyneuropathy
- Glycogen storage disease type 1A
- Primary hyperoxaluria type 1

α 1 - antitrypsin deficiency

Diagnosis

Autosomal recessive disease.

A diagnosis is most suspected in patients with early onset of COPD, with or without elevated liver enzymes.

Liver Transpl. 2016 Mar 6

Management and liver transplantation

End-stage liver disease related to A1AT deficiency is the most common inherited metabolic indication leading to liver transplantation in children and adults.

Survival after LT has been shown to be good, with 1-year, 3-year and 5-year survival rates around 87%, 79% and77% in adult patients.

J Med Genet. 2016 Feb 1

Metabolic disorders that may be indications for liver transplantation

- Nonalcoholic fatty liver disease
- Hereditary hemochromatosis
- Wilson’s disease
- α 1 - antitrypsin deficiency
- **Familial amyloidotic polyneuropathy**
- Glycogen storage disease type 1A
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Familial amyloidotic polyneuropathy

Familiar amyloidotic ployneuropathy

Autosomal dominant inheritance, resulting into multi-systemic disease.

It involves production of an abnormal protein by the liver(transthyretin), which is deposited in the autonomic nerves.

Symptoms: (difficulty walking, blood pressure and digestive disturbances, heart failure etc).

Expert Opin Pharmacother. 2016 Mar 10:1-12.

Familiar amyloidotic ployneuropathy

Liver function is absolutely normal.

So that, the patient who himself undergoes liver transplantation donates his liver to another recipient (domino effect).

One of the necessary conditions for recipients of FAP domino liver grafts is that they be older than 55 years, to minimize their risk of developing the disease.

J Proteomics. 2015 Sep 8;127(Pt B):234-46

Metabolic disorders that may be indications for liver transplantation

- Nonalcoholic fatty liver disease
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- **Glycogen storage disease type 1A**
- Primary hyperoxaluria type 1

Glycogen storage disease type 1A

Glycogen storage disease type 1A

Autosomal recessive disease, seen in one of 100.000 live births.

Inherited abnormalities of enzyme activity resulting in defects of glycogen synthesis or breakdown.

J Inherit Metab Dis. 2015 May;38(3):521-7

Glycogen storage disease type 1A

Patients have increased risk for developing liver adenomas typically developing in the second or third decades of life.

J Inherit Metab Dis. 2015 May;38(3):521-7

Glycogen storage disease type 1A

LT is required in patients with large unresectable adenomas to prevent complications such as HCC.

The outcome after LT for type 1 GSD is excellent.

Not only does LT result into the removal of the risk for HCC or other adenoma-complications, it also removes the underlying metabolic abnormality.

J Diabetes Metab Disord. 2013 Jun 6;12(1):25.

Metabolic disorders that may be indications for liver transplantation

- Nonalcoholic fatty liver disease
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- **Primary hyperoxaluria type 1**

Primary hyperoxaluria type 1

Primary hyperoxaluria type 1

Autosomal recessive disease associated with enzymatic defects resulting in enhanced conversion of glyoxalate into oxalate.

LT accompanies kidney transplantation in the setting of renal failure for future protection of the transplanted renal graft.

Gene Ther. 2016 Feb;23(2):129-34

Primary hyperoxaluria type 1

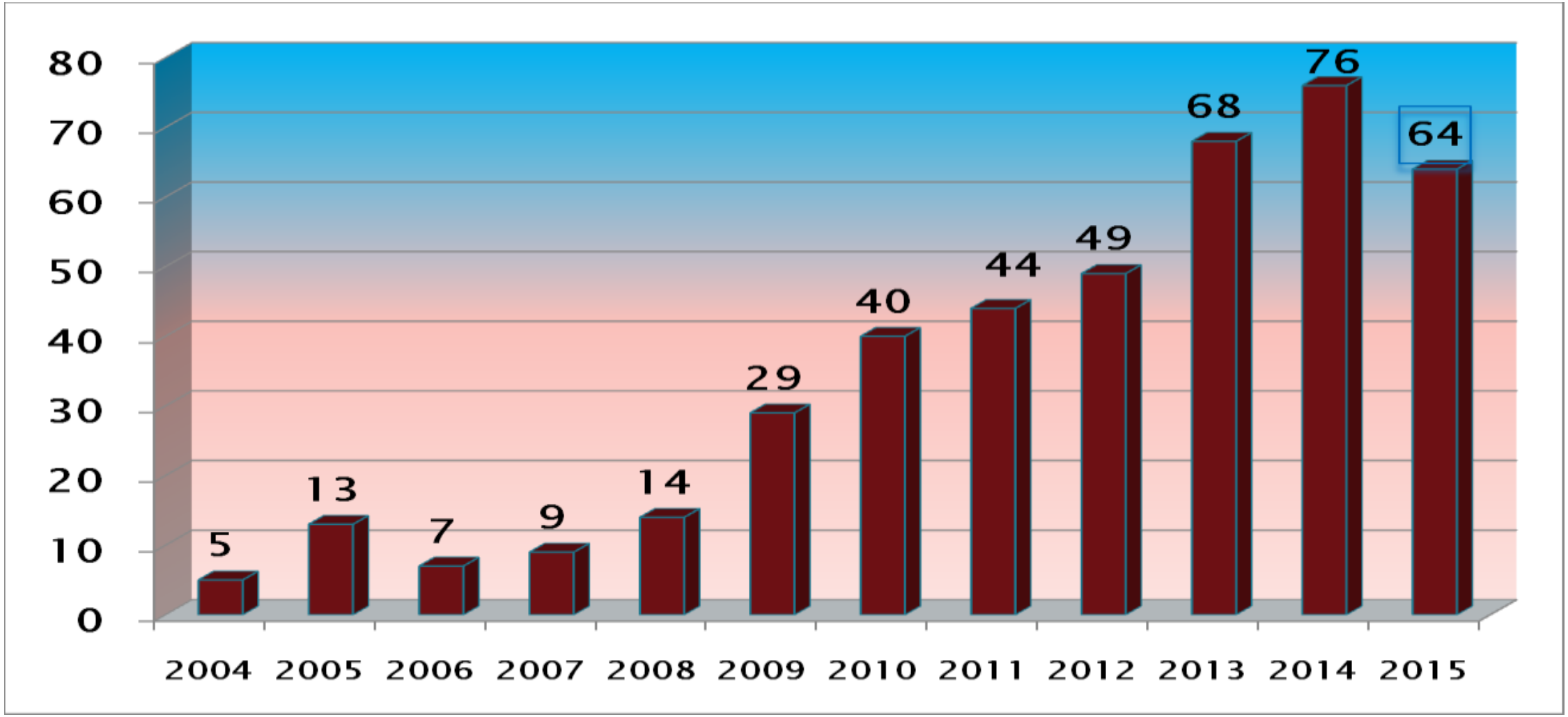
Pre-emptive liver transplantation (without renal transplantation) in stages with chronic renal insufficiency, not yet requiring renal transplantation, has been associated with improved growth and renal function.

Mol Ther. 2016 Jan 13

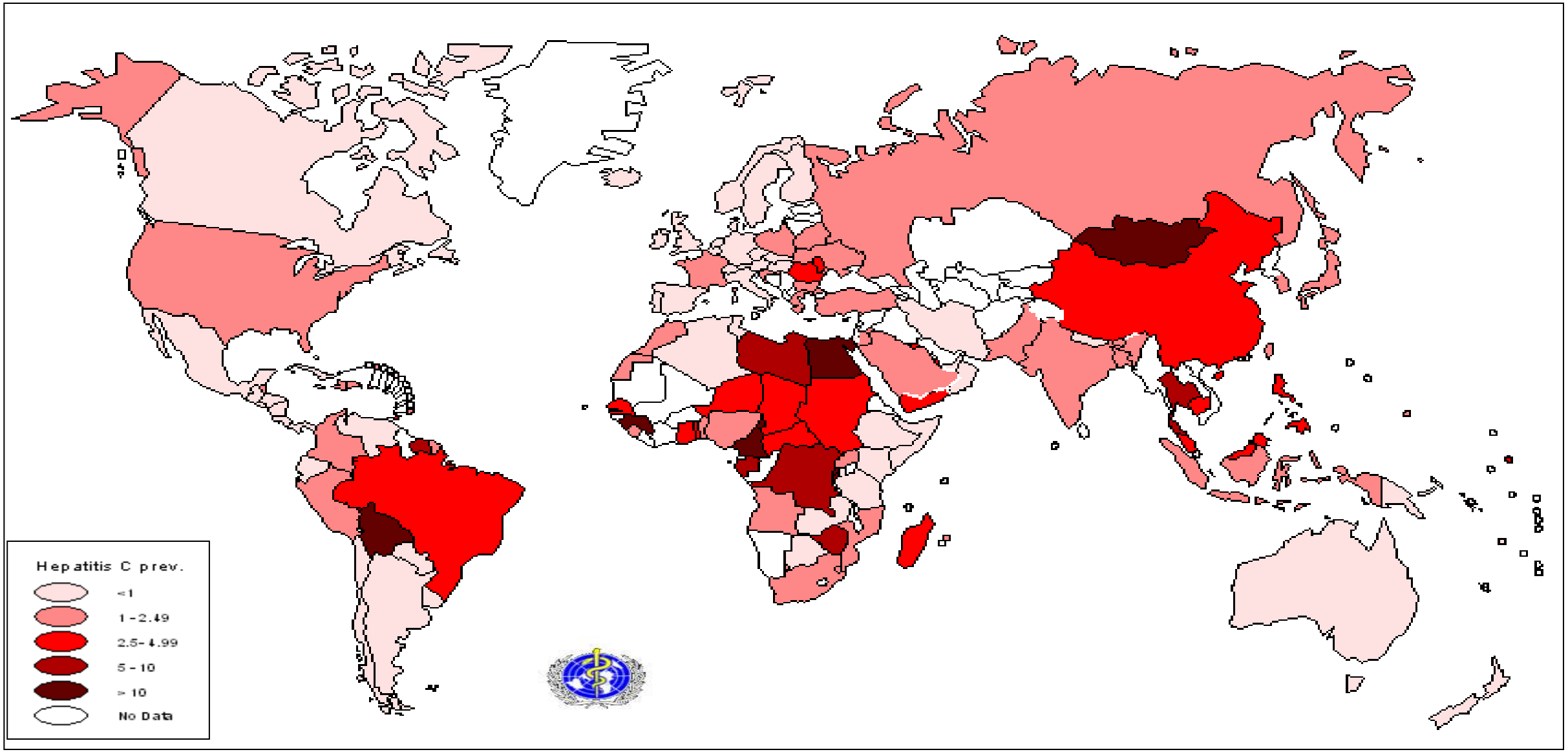
Mansoura Experience
Living Donor Liver Transplant
427 cases

Mansoura experience.

LIVER TRANSPLANTATION 427 cases



GLOBAL PREVALENCE OF HEPATITIS C



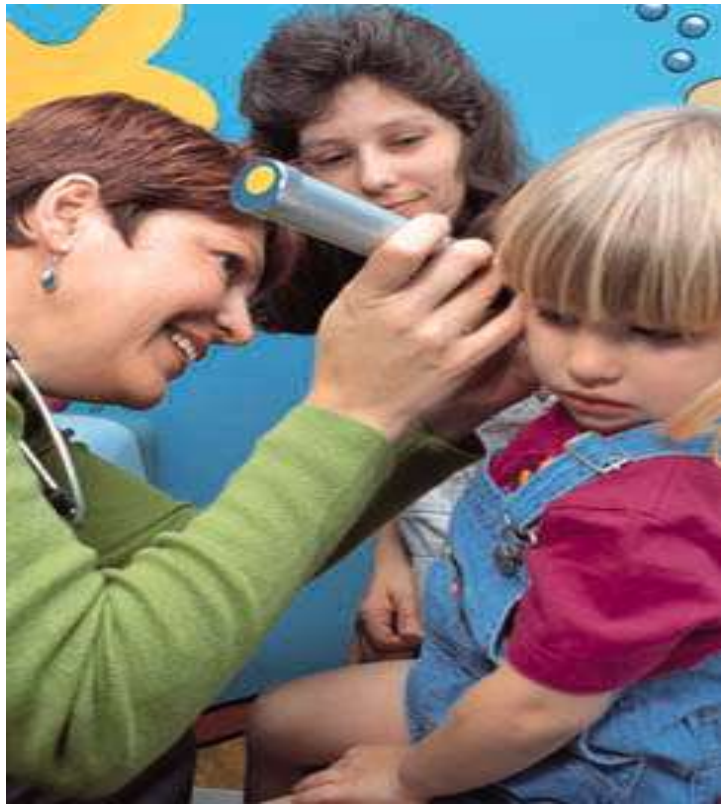
Drug addiction

Drug addiction

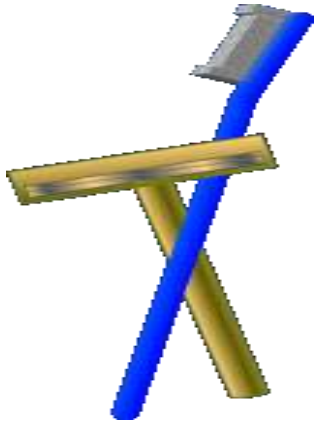
Tattooing

Tooth instruments

Hemodialysis machines



Instruments



Acupuncture

Contaminated syringes


10 17:34


امام المدخل الرئيسى لإحدى محطات مياه الشرب
11 17:26

Economist Intelligence Unit

The Economist

THE SILENT PANDEMIC

TACKLING HEPATITIS C WITH POLICY INNOVATION

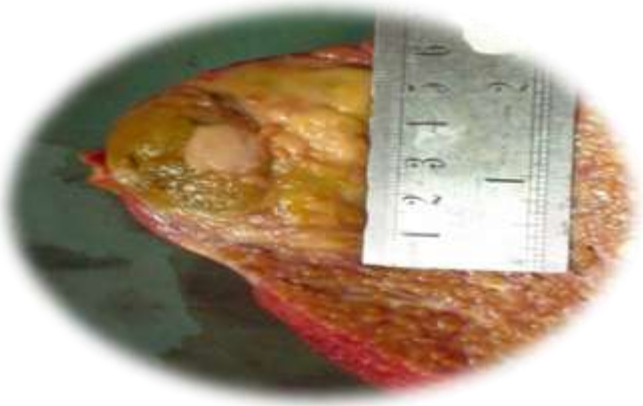
A report from the Economist Intelligence Unit.

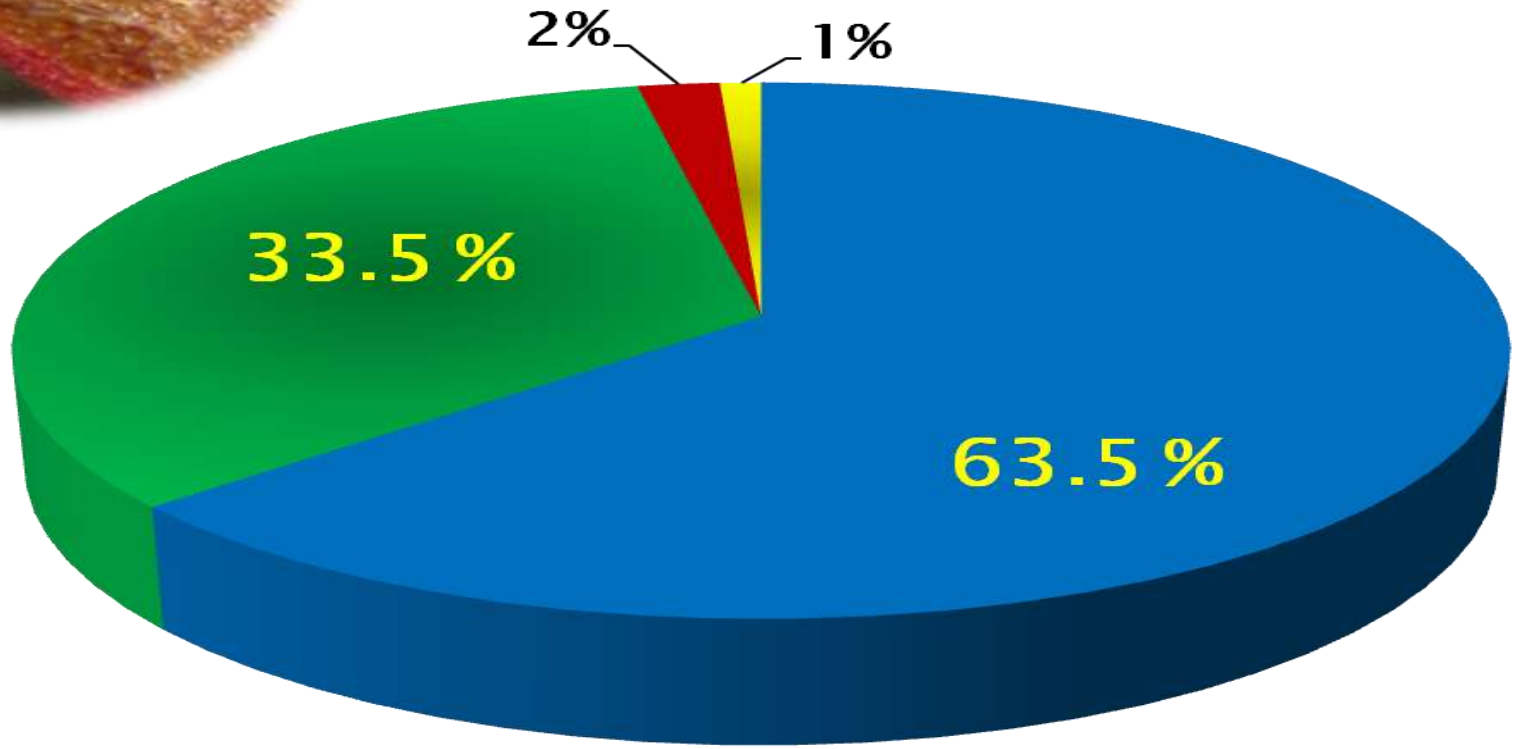
In Egypt, 150.000 – 170.000 new cases of HCV per year.

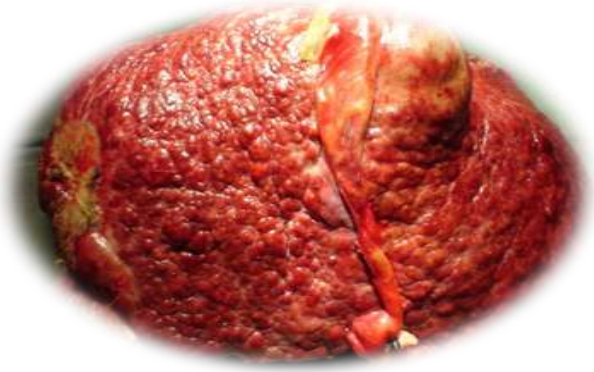
F DeWolfe Miller. The Economist 2015

LDLT Mansoura Experience

(427 case)

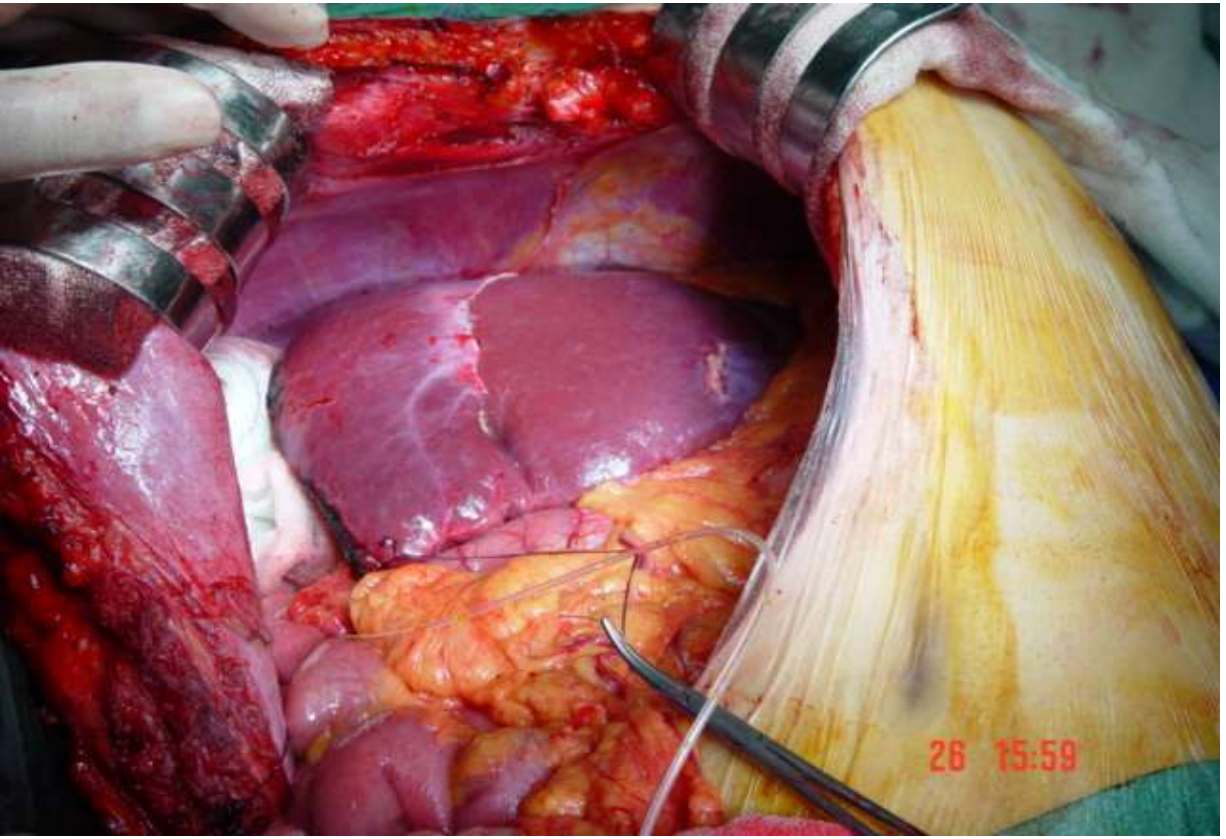






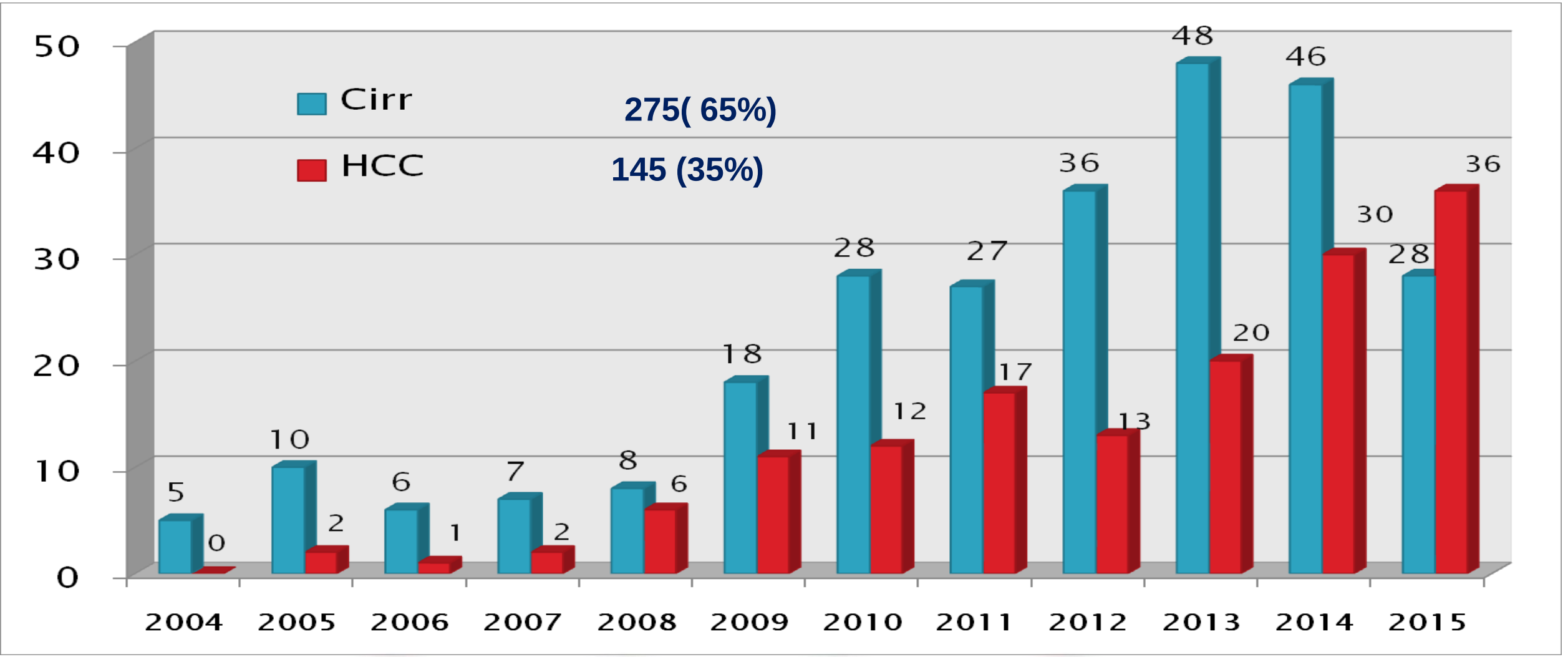
Mean age(46.67 Y)

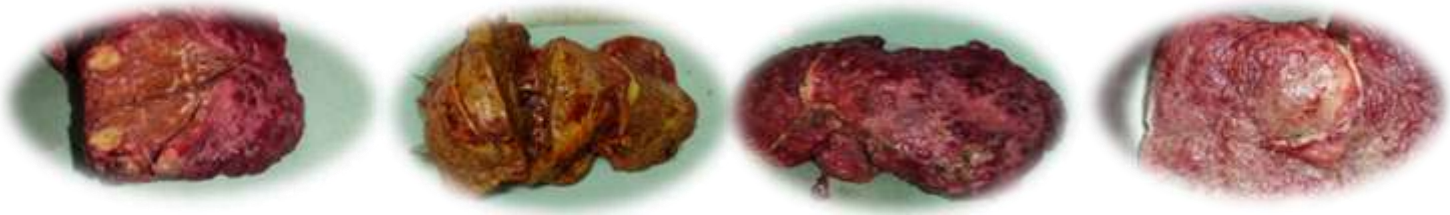
كبد سليم

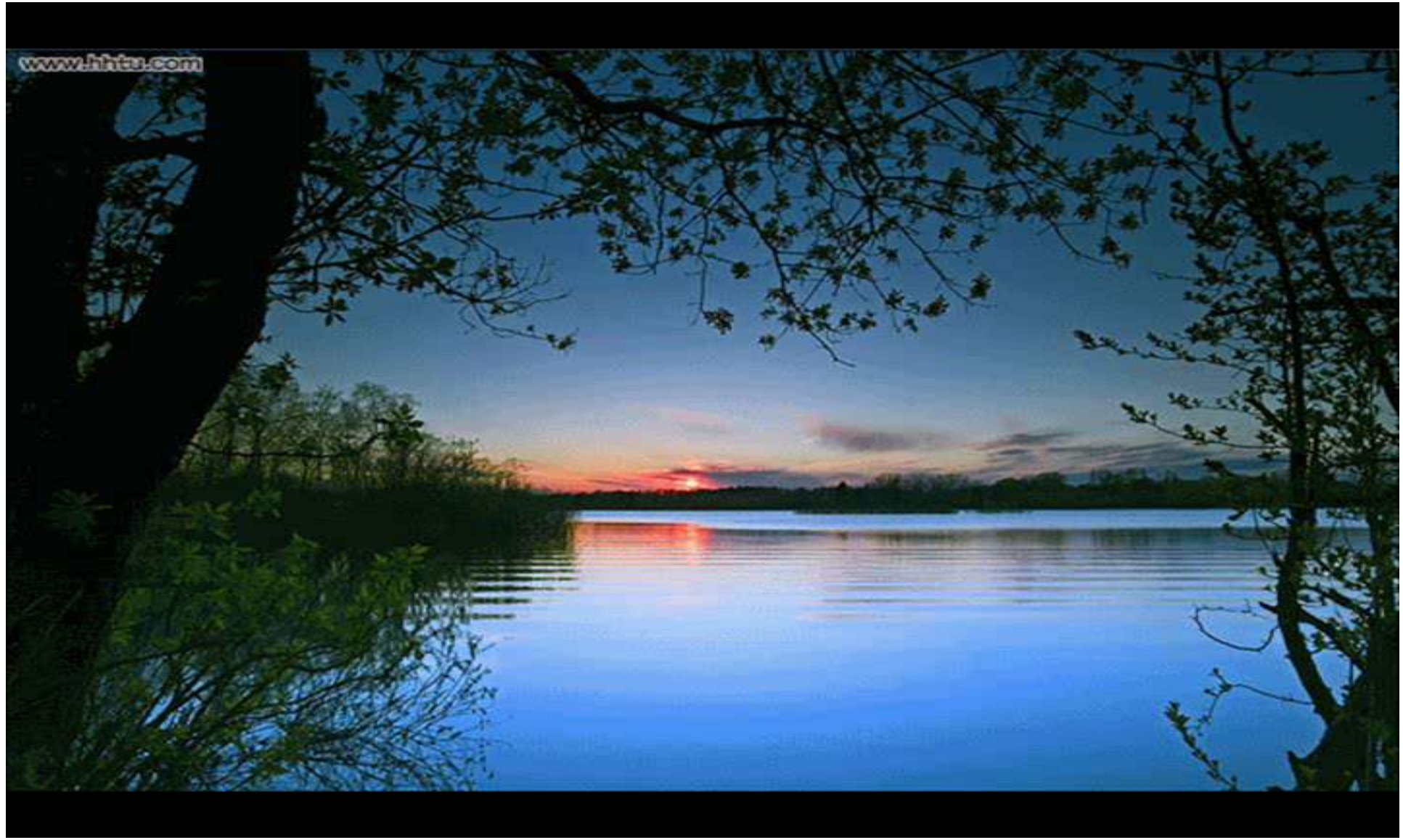


كبد متليف

LIVER TRANSPLANTATION 427 cases Indication






www.hhtu.com


Thank You